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Janet Sleath

Attorney Docket No. 11000/1037
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BOX PATENT APPLICATION - FEE
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Washington, D.C. 20231

UTILITY PATENT APPLICATION TRANSMITTAL LETTER UNDER 37 CFR 1.53(b)

Sir:

Transmitted herewith for filing is the patent application of **Lorna Strachan, Matthew Sleeman, Nevin Abernethy, Rene Onrust, Anand Kumble, and Greg Murison**

For: **COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE**

[X] 22 pages of specification and claims
[X] 18 pages of Sequence Listing
[X] Statement for Sequence Listing Transmittal
[X] ASCII Computer Disk Sequence pursuant to 37 CFR 1.821(f). It is believed that the content of the paper sequence listing and the computer readable sequence listing are the same.
[X] Combined Declaration and Power of Attorney (unsigned)
[X] Small Entity Statement (unsigned)

CLAIMS AS FILED

For	Number Filed		Number Extra	Rate	Basic Fee $ 380.00
Total Claims	19	- 20	= 0	x $ 9.00	= $ 00.00
Independent Claims	17	- 3	= 14	x $ 39.00	= $ 546.00
Multiple Dependent Claim Fee				$260.00	$ 00.00

Total Filing Fee $ 926.00
Assignment Recording Fee ($40.00) $ .00
TOTAL FEE $ 926.00

[X] The filing fee is **NOT** enclosed, but will be paid at the time the formal documents are submitted. Applicants want to assure, however, that the filing date of March 25, 1999 is assigned to this application. The Commissioner is therefor authorized to charge any fees which may be required **in connection with the assignment of a filing date for this application** to Deposit Account No. 19-3555. A duplicate copy of this sheet is enclosed.

[ ] Please charge $________ to Deposit Account No. __________.

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PATENT APPLICATION

Applicant	:	Lorna Strachan et al.
Application	:	09/_______
Filed	:	March 25, 1999
For	:	**COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE**
Attorney Docket No.	:	11000/1037

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(c))--SMALL BUSINESS CONCERN

I hereby declare that I am

[ ] the owner of the small business concern identified below.

[X] an official of the small business concern empowered to act on behalf of the concern identified below.

NAME OF CONCERN: Genesis Research & Development Corporation Limited

ADDRESS OF CONCERN: 1 Fox Street
Parnell, New Zealand 1001

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties control or have the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled **COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE** by inventors Lorna Strachan, Matthew Sleeman, Nevin Abernethy, Rene Onrust, Anand Kumble, and Greg Murison described in:

[X] the specification filed herewith.
[ ] application no. 09/________ filed on March 25, 1999.
[ ] patent no. , issued .

If the rights held by the above-entitled small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27.)

FULL NAME:

ADDRESS:

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b).)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: James D. Watson

TITLE OF PERSON OTHER THAN OWNER: Chief Executive Officer

ADDRESS OF PERSON SIGNING: 1 Fox Street
Parnell, New Zealand 1001

SIGNATURE ______________________ DATE ______________________

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COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE

Technical Field of the Invention

This invention relates to genes encoding proteins expressed in lymph node stromal cells from flaky skin (*fsn* -/-) mice and their use in therapeutic methods.

Background of the Invention

Lymph vessels and nodes are important components of the body's immune system. Lymph nodes are small lymphatic organs that are located in the path of lymph vessels. Large molecules and cells, including foreign substances, enter into the lymphatic vessels and, in circulating through these vessels, pass through the lymph nodes. Here, any foreign substances are concentrated and exposed to lymphocytes. This triggers a cascade of events that constitute an immune response, protecting the body from infection and from cancer.

Lymph nodes are surrounded by a dense connective tissue network that forms a supporting capsule. This network extends into the body of the lymph node, forming an additional framework of support. Throughout the remainder of the organ, a fine meshwork can be identified that comprises reticular fibres and the reticular cells that produce and surround the fibres. These features provide a support for the main functional cells of the lymphatic system, which are T- and B-lymphocytes. Additional cell types found in lymph nodes include macrophages, follicular dendritic cells, and endothelial cells that line the blood vessels servicing the node.

The cells within lymph nodes communicate with each other in order to defend the body against foreign substances. When a foreign substance, or antigen, is present, it is detected by macrophages and follicular dendritic cells that take up and process the antigen, and display parts of it on their cell surface. These cell surface antigens are then presented to T- and B-lymphocytes, causing them to proliferate and differentiate into activated T-lymphocytes and plasma cells, respectively. These cells are released into the circulation in order to seek out and destroy antigen. Some T- and B-lymphocytes will

also differentiate into memory cells. Should these cells come across the same antigen at a later date, the immune response will be more rapid.

Once activated T- and B-lymphocytes are released into the circulation, they can perform a variety of functions that leads to the eventual destruction of antigen. Activated T-lymphocytes can differentiate into cytotoxic lymphocytes (also known as killer T-cells) which recognise other cells that have foreign antigens on their surface and kill the cell by causing them to lyse. Activated T-lymphocytes can also differentiate into helper T-cells which will then secrete proteins in order to stimulate B-lymphocytes, and other T-lymphocytes, to respond to antigens. In addition, activated T-lymphocytes can differentiate into suppressor T-cells which secrete factors that suppress the activity of B-lymphocytes. Activated B-lymphocytes differentiate into plasma cells, which synthesise and secrete antibodies that bind to foreign antigens. The antibody-antigen complex is then detected and destroyed by macrophages, or by a group of blood constituents known as complement.

Lymph nodes can be dissociated and the resulting cells grown in culture. Cells that adhere to the tissue culture dishes can be maintained for some length of time and are known as stromal cells. The cultured cells are a heterogeneous population and can be made up of most cells residing within lymph nodes, such as reticular cells, follicular dendritic cells, macrophages and endothelial cells. It is well known that bone marrow stromal cells play a critical role in homing, growth and differentiation of hematopoietic progenitor cells. Proteins produced by stromal cells are necessary for the maintenance of plasma cells *in vitro*. Furthermore, stromal cells are known to secrete factors and present membrane bound receptors that are necessary for the survival of lymphoma cells.

An autosomal recessive mutation, designated flaky skin (*fsn* -/-), has been described in the inbred A/J mouse strain (The Jackson Laboratory, Bar Harbour, ME). The mice have a skin disorder similar to psoriasis in humans. Psoriasis is a common disease affecting 2% of the population, which is characterised by a chronic inflammation associated with thickening and scaling of the skin. Histology of skin lesions shows increased proliferation of the cells in the epidermis, the uppermost layer of skin, together with the abnormal presence of inflammatory cells, including lymphocytes, in the dermis, the layer of skin below the epidermis. While the cause of the disease is unclear, psoriasis

is associated with a disturbance of the immune system involving T lymphocytes. The disease occurs more frequently in family members, indicating the involvement of a genetic factor as well. Mice with the *fsn* gene mutation have not only a psoriatic-like skin disease but also other abnormalities involving cells of the immune and hemopoeitic system. These mice have markedly increased numbers of lymphocytes associated with enlarged lymphoid organs, including the spleen and lymph nodes. In addition, their livers are enlarged, and the mice are anaemic. Genes and proteins expressed in abnormal lymph nodes of *fsn-/-* mice may thus influence the development or function of cells of the immune and hemopoeitic system, the response of these cells in inflammatory disorders, and the responses of skin and other connective tissue cells to inflammatory signals. There is a need in the art to identify genes encoding proteins that function to modulate all cells of the immune system. These proteins from normal or abnormal lymph nodes may be useful in modifying the immune responses to tumour cells or infectious agents such as bacteria, viruses, protozoa and worms. Such proteins may be useful in disorders where the immune system initiates unfavourable reactions to the body, including Type I hypersensitivity reactions (such as hay fever, eczema, allergic rhinitis and asthma), and Type II hypersensitivity reactions (such as transfusion reactions and haemolytic disease of newborns). Other unfavourable reactions are initiated during Type III reactions, which are due to immune complexes forming in infected organs during persistent infection or in the lungs following repeated inhalation of materials from moulds, plants or animals, and in Type IV reactions in diseases such as leprosy, schistosomiasis and dermatitis.

Novel proteins of the immune system may also be useful in treating autoimmune diseases where the body recognises itself as foreign. Examples of such diseases include rheumatoid arthritis, Addison's disease, ulcerative colitis, dermatomyositis and lupus. Such proteins may also be useful during tissue transplantation, where the body will often recognise the transplanted tissue as foreign and attempt to kill it, and also in bone marrow transplantation when there is a high risk of graft-verus-host disease where the transplanted cells attack their host cells, often causing death..

There thus remains a need in the art for the identification and isolation of genes encoding proteins expressed in cells of the immune system for use in the development of

therapeutic agents for the treatment of disorders including those associated with the immune system.

Summary of the Invention

The present invention provides polypeptides expressed in lymph node stromal cells of *fsn* -/- mice, together with polynucleotides encoding such polypeptides, expression vectors and host cells comprising such polynucleotides, and methods for their use.

In specific embodiments, isolated polypeptides are provided that comprise an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 11-20, and variants of such sequences, as defined herein, together with polynucleotides encoding such polypeptides. Isolated polypeptides which comprise at least a functional portion of a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 11-20; and (b) variants of a sequence of SEQ ID NO: 11-20, as defined herein, are also provided.

In other embodiments, the present invention provides isolated polynucleotides comprising a nucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-10; (b) complements of sequences recited in SEQ ID NO: 1-10; (c) reverse complements of sequences recited in SEQ ID NO: 1-10; (d) reverse sequences of sequences recited in SEQ ID NO: 1-10; and (e) variants of the sequences of (a) – (d), as defined herein.

In related embodiments, the present invention provides expression vectors comprising the above polynucleotides, together with host cells transformed with such vectors.

As detailed below, the isolated polynucleotides and polypeptides of the present invention may be usefully employed in the preparation of therapeutic agents for the treatment of immunological disorders.

Methods for modulating the growth of blood vessels, and for the treatment of disorders such as inflammatory disorders, disorders of the immune system, cancer, tumour-necrosis factor-mediated disorders, and viral disorders are also provided.

Examples of such disorders include HIV-infection; epithelial, lymphoid, myeloid, stromal and neuronal cancers; arthritis; inflammatory bowel disease; and cardiac failure.

The above-mentioned and additional features of the present invention, together with the manner of obtaining them, will be best understood by reference to the following more detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Detailed Description of the Invention

In one aspect, the present invention provides polynucleotides isolated from lymph node stromal cells of *fsn* -/- mice and isolated polypeptides encoded by such polynucleotides.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments. Anti-sense polynucleotides and techniques involving anti-sense polynucleotides are well known in the art and are described, for example, in Robinson-Benion et al. (1995), Antisense techniques, *Methods in Enzymol.* 254(23): 363-375 and Kawasaki et al. (1996), *Artific. Organs* 20 (8): 836-848.

In specific embodiments, the inventive polynucleotides comprise a DNA sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-10, and variants of the sequences of SEQ ID NO: 1-10, as defined below. The present invention also encompasses polynucleotide sequences that differ from the disclosed sequences but which, due to the degeneracy of the genetic code, encode a polypeptide which is the same as that encoded by a polynucleotide sequence disclosed herein.

Polynucleotides that comprise complements of such DNA sequences, reverse complements of such DNA sequences or reverse sequences of such DNA sequences, together with variants of such sequences, are also provided. The definition of the terms "complement", "reverse complement" and "reverse sequence", as used herein, is best illustrated by the following example. For the sequence 5' AGGACC 3', the complement, reverse complement and reverse sequence are as follows:

complement	3' TCCTGG 5'
reverse complement	3' GGTCCT 5'
reverse sequence	5' CCAGGA 3'.

In another aspect, the present invention provides isolated polypeptides encoded, or partially encoded, by the above polynucleotides. The term "polypeptide", as used herein, encompasses amino acid chains of any length including full length proteins, wherein amino acid residues are linked by covalent peptide bonds. Polypeptides of the present invention may be naturally purified products, or may be produced partially or wholly using recombinant techniques. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a nucleotide sequence which includes the partial isolated DNA sequences of the present invention. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20 and variants of such sequences.

All of the polynucleotides and polypeptides described herein are isolated and purified, as those terms are commonly used in the art.

As used herein, the term "variant" covers any sequence which has at least about 40%, more preferably at least about 60%, more preferably yet at least about 75% and most preferably at least about 90% identical residues (either nucleotides or amino acids) to a sequence of the present invention. The percentage of identical residues is determined by aligning the two sequences to be compared, determining the number of identical residues in the aligned portion, dividing that number by the total length of the inventive, or queried, sequence and multiplying the result by 100.

Polynucleotide or polypeptide sequences may be aligned, and percentage of identical nucleotides in a specified region may be determined against another polynucleotide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms. The similarity of polypeptide sequences may be examined using the BLASTP or FASTX algorithms. Both the BLASTN and BLASTP software are available on the NCBI anonymous FTP server (ftp://ncbi.nlm.nih.gov) under /blast/executables/. The BLASTN algorithm version 2.0.4 [Feb-24-1998], set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN and BLASTP, is described at NCBI's website at URL http://www.ncbi.nlm.nih.gov/BLAST/newblast.html and in the publication of Altschul, Stephen F., et al. (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", *Nucleic Acids Res. 25*:3389-3402. The computer algorithm FASTA is available on the Internet at the ftp site ftp://ftp.virginia.edu/pub/fasta/. Version 2.0u4, February 1996, set to the default parameters described in the documentation and distributed with the algorithm, is preferred for use in the determination of variants according to the present invention. The use of the FASTA algorithm is described in W.R. Pearson and D.J. Lipman, "Improved Tools for Biological Sequence Analysis," *Proc. Natl. Acad. Sci. USA 85*:2444-2448 (1988) and W.R. Pearson, "Rapid and Sensitive Sequence Comparison with FASTP and FASTA," *Methods in Enzymology 183*:63-98 (1990). The use of the FASTX algorithm is described in Pearson, W.R., Wood, T., Zhang, Z. and Miller, W., "Comparison of DNA sequences with protein sequences," *Genomics 46*(1):24-36 (1997).

The following running parameters are preferred for determination of alignments and similarities using BLASTN that contribute to the E values and percentage identity: Unix running command: blastall -p blastn -d embldb -e 10 -G 1 -E 1 -r 2 -v 50 -b 50 -i queryseq –o results; and parameter default values:

-p Program Name [String]

-d Database [String]

-e Expectation value (E) [Real]

-G Cost to open a gap (zero invokes default behavior) [Integer]

-E Cost to extend a gap (zero invokes default behavior) [Integer]

-r Reward for a nucleotide match (blastn only) [Integer]

-v Number of one-line descriptions (V) [Integer]

-b Number of alignments to show (B) [Integer]

-i Query File [File In]

-o BLAST report Output File [File Out] Optional

For BLASTP the following running parameters are preferred: blastall –p blastp –d swissprotdb –e 10 –G 1 –E 1 –v 50 –b 50 –i queryseq –o results

-p Program Name [String]

-d Database [String]

-e Expectation value (E) [Real]

-G Cost to open a gap (zero invokes default behavior) [Integer]

-E Cost to extend a gap (zero invokes default behavior) [Integer]

-v Number of one-line descriptions (v) [Integer]

-b Number of alignments to show (b) [Integer]

-I Query File [File In]

-o BLAST report Output File [File Out] Optional

The "hits" to one or more database sequences by a queried sequence produced by BLASTN, BLASTP, FASTA, or a similar algorithm, align and identify similar portions of sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

The BLASTN and FASTA algorithms also produce "Expect" values for alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database, such as the preferred EMBL database, indicates true similarity. For example, an E value of 0.1 assigned to a hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by chance. By this

criterion, the aligned and matched portions of the sequences then have a probability of 90% of being the same. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN or FASTA algorithm.

According to one embodiment, "variant" polynucleotides, with reference to each of the polynucleotides of the present invention, preferably comprise sequences having the same number or fewer nucleic acids than each of the polynucleotides of the present invention and producing an E value of 0.01 or less when compared to the polynucleotide of the present invention. That is, a variant polynucleotide is any sequence that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at the default parameters. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at the default parameters.

Variant polynucleotide sequences will generally hybridize to the recited polynucleotide sequence under stringent conditions. As used herein, "stringent conditions" refers to prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65 °C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65 °C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65 °C.

As used herein, the term "*x*-mer," with reference to a specific value of "*x*," refers to a sequence comprising at least a specified number ("*x*") of contiguous residues of any of the polynucleotides or polypeptides identified as SEQ ID NO: 1-20. The value of *x* may be from about 20 to about 600, depending upon the specific sequence.

Polynucleotides and polypeptides of the present invention comprehend polynucleotides and polypeptides comprising at least a specified number of contiguous residues (*x*-mers) of any of the polynucleotides or polypeptides identified as SEQ ID NO: 1-20 or their variants. According to preferred embodiments, the value of *x* is preferably at least 20, more preferably at least 40, more preferably yet at least 60, and most

preferably at least 80. Thus, polynucleotides and polypeptides of the present invention include polynucleotides or polypeptides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer a 250-mer, or a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide or polypeptide identified as SEQ ID NO: 1-20 or a variant thereof.

The inventive polynucleotides may be isolated by high throughput sequencing of cDNA libraries prepared from lymph node stromal cells of *fsn* -/- mice as described below in Example 1. Alternatively, oligonucleotide probes based on the sequences provided in SEQ ID NO: 1-10 can be synthesized and used to identify positive clones in either cDNA or genomic DNA libraries from lymph node stromal cells of *fsn* -/- mice by means of hybridization or polymerase chain reaction (PCR) techniques. Probes can be shorter than the sequences provided herein but should be at least about 10, preferably at least about 15 and most preferably at least about 20 nucleotides in length. Hybridization and PCR techniques suitable for use with such oligonucleotide probes are well known in the art (see, for example, Mullis, et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989; Maniatis et al., *Molecular Cloning – A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989). Positive clones may be analyzed by restriction enzyme digestion, DNA sequencing or the like.

In addition, DNA sequences of the present invention may be generated by synthetic means using techniques well known in the art. Equipment for automated synthesis of oligonucleotides is commercially available from suppliers such as Perkin Elmer/Applied Biosystems Division (Foster City, CA) and may be operated according to the manufacturer's instructions.

Polypeptides of the present invention may be produced recombinantly by inserting a DNA sequence that encodes the polypeptide into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the

host cells employed are *E. coli*, insect, yeast or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20 and variants thereof. As used herein, the "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity. Such functional portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Functional portions of the inventive polypeptides may be identified by first preparing fragments of the polypeptide, by either chemical or enzymatic digestion of the polypeptide or mutation analysis of the polynucleotide that encodes for the polypeptide, and subsequently expressing the resultant mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to determine which portions retain the biological activity of the full-length polypeptide.

Portions and other variants of the inventive polypeptides may be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see, for example, Kunkel, T.,

Proc. Natl. Acad. Sci. USA 82:488-492, 1985). Sections of DNA sequence may also be removed using standard techniques to permit preparation of truncated polypeptides.

Since the polynucleotide sequences of the present invention have been derived from *fsn* -/- mouse lymph node stromal cells, they likely encode proteins that have important role(s) in growth and development of the immune system, and in responses of the immune system to tissue injury and inflammation as well as other disease states. Some of the polynucleotides contain sequences that code for signal sequences, or transmembrane domains, which identify the protein products as secreted molecules or receptors. Such protein products are likely to be growth factors, cytokines, or their cognate receptors. The polypeptide sequence of SEQ ID NO: 13 has more than 25% similarity to known members of the tumour necrosis factor (TNF) receptor family of proteins and is thus likely to have similar biological functions.

In particular, the inventive polypeptides may have important roles in processes such as: modulation of immune responses; differentiation of precursor immune cells into specialized cell types; cell migration; cell proliferation and cell-cell interaction. The polypeptides may be important in the defence of the body against infectious agents, and thus be of importance in maintaining a disease-free environment. These polypeptides may act as modulators of skin cells, especially since immune cells are known to infiltrate skin during tissue insult, causing growth and differentiation of skin cells. In addition, these proteins may be immunologically active, making them important therapeutic targets in a whole range of disease states.

In one aspect, the present invention provides methods for using one or more of the inventive polypeptides or polynucleotides to treat disorders in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human.

In this aspect, the polypeptide or polynucleotide is generally present within a pharmaceutical composition or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. Vaccines may comprise one or more of the above polypeptides and a non-specific immune response amplifier, such as an adjuvant or a liposome, into which the polypeptide is incorporated.

Alternatively, a vaccine or pharmaceutical composition of the present invention may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated *in situ*. In such vaccines and pharmaceutical compositions, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, and bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminator signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other poxvirus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic, or defective, replication competent virus. Techniques for incorporating DNA into such expression systems are well known in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intradermal, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg per kg of host, and preferably from about 100 pg to about 1 μg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 ml to about 5 ml.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such

as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of adjuvants may be employed in the vaccines derived from this invention to non-specifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a non-specific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *M. tuberculosis*. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories, Detroit, MI), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and Quil A.

The polynucleotides of the present invention may also be used as markers for tissue, as chromosome markers or tags, in the identification of genetic disorders, and for the design of oligonucleotides for examination of expression patterns using techniques well known in the art, such as the microarray technology available from Synteni (Palo Alto, CA). Partial polynucleotide sequences disclosed herein may be employed to obtain full length genes by, for example, screening of DNA expression libraries using hybridization probes or PCR primers based on the inventive sequences.

The proteins provided by the present invention may additionally be used in assays to determine biological activity, to raise antibodies, to isolate corresponding ligands or receptors, in assays to quantify levels of protein or cognate corresponding ligand or receptor, as anti-inflammatory agents, and in compositions for the treatment of diseases of skin, connective tissue and the immune system.

Example 1

ISOLATION OF cDNA SEQUENCES FROM LYMPH NODE STROMAL CELL EXPRESSION LIBRARIES

The cDNA sequences of the present invention were obtained by high-throughput sequencing of cDNA expression libraries constructed from rodent *fsn* -/- lymph node stromal cells as described below.

cDNA Libraries from Lymph Node Stromal Cells (MLSA and MLSE)

Lymph nodes were removed from flaky skin *fsn* -/- mice, the cells dissociated and the resulting single cell suspension placed in culture. After four passages, the cells were harvested. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. A cDNA expression library (referred to as the MLSA library) was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene, La Jolla, CA). A second cDNA expression library, referred to as the MLSE library, was prepared exactly as above except that the cDNA was inserted into the mammalian expression vector pcDNA3 (Invitrogen, Carlsbad CA).

The nucleotide sequence of the cDNA clone isolated from the MLSE library is given in SEQ ID NO: 1, with the corresponding amino acid sequence being provided in SEQ ID NO: 11. The nucleotide sequences of the cDNA clones isolated from the MLSA library are given in SEQ ID NO: 2-10, with the corresponding amino acid sequences being provided in SEQ ID NO: 12-20, respectively.

Subtracted cDNA Library from flaky skin Lymph Node Stromal Cells (MLSS)

Stromal cells from flaky skin mice lymph nodes and 3T3 fibroblasts were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA from both populations was isolated using TRIzol Reagent (Gibco BRL Life Technologies, Gaitherburg, MD) and used to obtain mRNA using either a Poly (A) Quik mRNA isolation kit (Stratagene, La Jolla, CA) or Quick Prep(R) Micro mRNA

purification kit (Pharmacia, Uppsala, Sweden). Double-stranded cDNA from flaky skin lymph node stromal cell mRNA was prepared by reverse transcriptase synthesis using a lambda ZAP cDNA library synthesis kit (Stratagene) that had been ligated with *Eco*RI adaptors and digested with *Xho*I to produce double-stranded fragments with *Eco*RI and *Xho*I overhanging ends.

Double-stranded cDNA from 3T3 fibroblasts was prepared using the Superscript II reverse transcriptase (BRL Life Technologies) followed by treatment with DNA polymerase I and RnaseH (BRL Life Technologies). Double-stranded 3T3 cDNA was then digested with restriction endonucleases *Alu*I and *Rsa*I (BRL Life Technologies) to produce blunt-ended fragments. A 20-fold excess of *Alu*I /*Rsa*I-digested 3T3 cDNA was hybridized with the *Eco*RI/*Xho*I flaky skin lymph node stromal cell cDNA in the following hybridisation solution: 50% formamide, 5xSSC, 10mM NaH_2PO_4 pH7.5, 1mM EDTA, 0.1% SDS, 200μg yeast tRNA (Boehringer Mannheim) at 37°C for 24 hours. Hybridized flaky skin lymph node stromal cell cDNA and 3T3 cDNA was then phenol/chloroform extracted and ethanol precipitated. The cDNA was size-fractionated over a Sepharose CL-2B gel filtration column as described in the Lambda ZAP cDNA library synthesis protocol (Stratagene). Flaky skin lymph node stromal cell-specific cDNA was preferentially ligated into ZAP express vector (Stratagene) by virtue of *Eco*RI/*Xho*I ends. Chimeric cDNA between flaky skin lymph node stromal cell cDNA and 3T3 cDNA would not be cloned due to non-compatible ends, and the subtracted cDNA library was packaged using Gigapack III Gold packaging extract (Stratagene).

EXAMPLE 2

CHARACTERIZATION OF ISOLATED cDNA SEQUENCES

The isolated cDNA sequences were compared to sequences in the EMBL DNA database using the computer algorithm BLASTN, and the corresponding predicted protein sequences (DNA translated to protein in each of 6 reading frames) were compared to sequences in the SwissProt database using the computer algorithm BLASTP. Specifically, comparisons of DNA sequences provided in SEQ ID NO: 1-10 to sequences in the EMBL (Release 58, March 1999) DNA database, and amino acid sequences provided in SEQ ID NO: 11-20 to sequences in the SwissProt (Release 37) and TREMBL

(Release 8 and updates until 23 January 1999) databases were made as of March 21, 1999. The cDNA sequences of SEQ ID NO: 1-10, and their corresponding predicted amino acid sequences (SEQ ID NO: 11-20, respectively) were determined to have less than 75% identical nucleotides or amino acid residues (determined as described above) to sequences in the EMBL and SwissProt databases using the computer algorithms BLASTN and BLASTP, respectively.

Isolated cDNA sequences and their corresponding predicted protein sequences, were computer analyzed for the presence of signal sequences identifying secreted molecules. Isolated cDNA sequences that have a signal sequence at a putative start site within the sequence are provided in SEQ ID NO: 4-6 and 9-10. The isolated cDNA sequences were also computer analyzed for the presence of transmembrane domains coding for putative membrane-bound molecules. Isolated cDNA sequences that have one or more transmembrane domain(s) within the sequence are provided in SEQ ID NO: 1-3, 7 and 8.

Using automated search programs to screen against sequences coding for known molecules reported to be of therapeutic and/or diagnostic use, the isolated cDNA sequence of SEQ ID NO: 3 was determined to encode a predicted protein sequence (SEQ ID NO: 13) that appears to be a member of the tumour necrosis factor (TNF) receptor family of proteins. A family member is here defined to have at least 25% identical amino acid residues in the translated polypeptide to a known protein or member of a protein family. Proteins of the TNF/NGF-receptor family are involved in the proliferation, differentiation and death of many cell types including B and T lymphocytes. Residues 18-55 of SEQ ID NO: 13 show a high degree of similarity to the Prosite motif for TNF/NGF receptor family (Banner D.W., d'Arcy A., Janes W., Gentz R., Schoenfeld H.-J., Broger C., Loetscher H., Lesslauer W. *Cell 73*:431-445 (1993). This motif contributes to the ligand binding domain of the molecule and is thus essential to its function. (Gruss H.J. and Dower S. Tumor necrosis factor ligand superfamily: involvement in the pathology of malignant lymphomas, *Blood 85*:3378-3404 (1995).

The polypeptide of SEQ ID NO: 13 is therefore likely to influence the growth, differentiation and activation of several cell types, and may be usefully developed as an

agent for the treatment of skin wounds, and the treatment and diagnosis of cancers, inflammatory diseases, and growth and developmental defects.

CLAIMS:

1. An isolated polypeptide comprising a sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20.

2. An isolated polypeptide comprising a sequence selected from the group consisting of:

   (a) sequences having at least 40% identical residues to a sequence provided in SEQ ID NO: 11-20 as determined using the computer algorithm BLASTP;

   (b) sequences having at least 60% identical residues to a sequence provided in SEQ ID NO: 11-20 as determined using the computer algorithm BLASTP;

   (c) sequences having at least 75% identical residues to a sequence provided in SEQ ID NO: 11-20 as determined using the computer algorithm BLASTP; and

   (d) sequences having at least 90% identical residues to a sequence provided in SEQ ID NO: 11-20 as determined using the computer algorithm BLASTP.

3. An isolated polynucleotide that encodes a polypeptide according to any one of claims 1 and 2.

4. An isolated polynucleotide comprising a sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-10.

5. An isolated polynucleotide comprising a sequence selected from the group consisting of:

   (a) complements of the sequence recited in SEQ ID NO: 1-10;

   (b) reverse complements of the sequence recited in SEQ ID NO: 1-10;

   (c) reverse sequences of the sequences recited in SEQ ID NO: 1-10;

   (d) sequences having at least 40% identical nucleotides to a sequence provided in SEQ ID NO: 1-10 as determined using the computer algorithm BLASTN;

   (e) sequences having at least 60% identical nucleotides to a sequence provided in SEQ ID NO: 1-10 as determined using the computer algorithm BLASTN;

   (f) sequences having at least 75% identical nucleotides to a sequence provided in SEQ ID NO: 1-10 as determined using the computer algorithm BLASTN; and

   (g) sequences having at least 90% identical nucleotides to a sequence provided in SEQ ID NO: 1-10 as determined using the computer algorithm BLASTN.

6. An isolated polynucleotide comprising a sequence selected from the group consisting of: (a) sequences that are a 200-mer of an isolated polynucleotide according to any one of claims 1, 2 and 5; (b) sequences that are a 100-mer of an isolated polynucleotide according to any one of claims 1, 2 and 5; and (c) sequences that are a 40-mer of an isolated polynucleotide according to any one of claims 1, 2 and 5.

7. An expression vector comprising an isolated polynucleotide according to any one of claims 3-6.

8. A host cell transformed with an expression vector according to claim 7.

9. An isolated polypeptide comprising at least a functional portion of a polypeptide having an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 11-20.

10. A pharmaceutical composition comprising an isolated polypeptide according to any one of claims 1 and 2.

11. A pharmaceutical composition comprising an isolated polynucleotide according to any one of claims 3-6.

12. A method for the treatment of an inflammatory disorder in a patient, comprising administering to the patient a composition comprising an isolated polypeptide according to any one of claims 1 and 2.

13. A method for modulating the growth of blood vessels in a patient, comprising administering to the patient a composition comprising an isolated polypeptide according to any one of claims 1 and 2.

14. A method for the treatment of an disorder of the immune system in patient, comprising administering to the patient a composition comprising an isolated polypeptide according to any one of claims 1 and 2.

15. A method for the treatment of cancer in a patient, comprising administering to the patient a composition comprising an isolated polypeptide according to any one of claims 1 and 2, wherein the cancer is selected from the group consisting of epithelial, lymphoid, myeloid, stromal and neuronal cancers.

16. A method for the treatment of a tumour necrosis factor-mediated disorder in a patient, comprising administering to the patient a composition comprising an

isolated polypeptide, the polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) a sequence of SEQ ID NO: 13;

(d) sequences having at least 40% identical residues to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP;

(e) sequences having at least 60% identical residues to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP;

(f) sequences having at least 75% identical residues to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP; and

(d) sequences having at least 90% identical residues to the sequence of SEQ ID NO: 13 as determined using the computer algorithm BLASTP.

17. The method of claim 16, wherein the tumour necrosis factor-mediated disorder is selected from the group consisting of arthritis, inflammatory bowel disease and cardiac failure.

18. A method for the treatment of a viral disorder in a patient, comprising administering to the patient a composition comprising an isolated polypeptide according to any one of claims 1 and 2.

19. The method of claim 19, wherein the viral disorder is HIV-infection.

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COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE

Abstract of the Disclosure

Isolated polynucleotides encoding polypeptides expressed in mammalian *fsn* -/- lymph node stromal cells are provided, together with expression vectors and host cells comprising such isolated polynucleotides. Methods for the use of such polynucleotides and polypeptides are also provided.

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As one of the below-named inventors, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe I am an original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled COMPOSITIONS ISOLATED FROM STROMAL CELLS AND METHODS FOR THEIR USE, the specification of which

[X] is attached hereto.

[ ] was filed on March 25, 1999 as Application No. 09/

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: **NONE.**

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application: **NONE.**

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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agctgctcga cagctgctgg catggccgtg ctcttgcaca tgcgccgctg tgggcatggg 1539
gattgctgtg cagcctcagc tgtgttgtgt ggctgctgat taaactgtcc cctaaacagc 1599
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 1630

<210> 5
<211> 1197
<212> DNA
<213> Mouse

<220>
<221> CDS
<222> (346)...(543)

<221> sig_peptide
<222> (346)...(420)

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acccccaaac tagtggactt tgaagttttc ttcccagccg gttccagcct cctggaacaa 180
ccatgtcgcc agttttgcgc gtgccaaatt cacggcgctg cccaagcgga gctgctatct 240
gaattctcct tggatgtggc aaagggaaat gaacgcaaaa ggtgccgctg gaagtgtccg 300
acctagagaa atatgtagac cggagccctg ttaccttcct ccagc atg gac ttc ctg 357
Met Asp Phe Leu
-25

gtt ctc ttc ttg ttc tac ttg gcc ttc tta ttg att tgt gtt gtc ctg 405
Val Leu Phe Leu Phe Tyr Leu Ala Phe Leu Leu Ile Cys Val Val Leu
-20 -15 -10

atc tgc atc ttc aca aaa agc cag cgt ttg aag gcc gtg gtc ctt gga 453
Ile Cys Ile Phe Thr Lys Ser Gln Arg Leu Lys Ala Val Val Leu Gly
-5 1 5 10

gga gca cag gta gca ctg gtc ctt ggg tac tgc ccg gat gtg aat act 501
Gly Ala Gln Val Ala Leu Val Leu Gly Tyr Cys Pro Asp Val Asn Thr
15 20 25

gtg tta ggt gct agt ctg gaa ggc tca caa gac aag ggg atg 543
Val Leu Gly Ala Ser Leu Glu Gly Ser Gln Asp Lys Gly Met
30 35 40

tgagtcttgt ctttaatcct ggcacttggg aggctgaggc ttcggggcca gttggggcta 603
catcgcaaga gcctgtgtcc aaacaaacaa aacgttgtct ttttgctttg agataggtcg 663
aataggtcga attttcaagg ttggcttttt aaacagtgtg taatgtctgt atttggttgt 723
gactcctgtt tgcctagaca tgcttgtagc aggtgtgaac tcaggaggac acaagtgacc 783
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ggggtcaaag caaagtgggg gcaagtagcc acgaaggggt tgacttggga ggaccctggg 903
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ggtagaaatg gaggtgttct ctacacctcc taaatcctag cacttaggaa gctgaggcag 1083
gattatgaat tccaggctag ctcgggttat gtaatgagac tgtttcaaac acagagcgga 1143
gccgaggaga tggctgggca gtcacagagc tgccgtgcaa ccagaactgg aggg 1197

<210> 6
<211> 1435
<212> DNA
<213> Mouse

<220>
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<222> (2)...(1015)

<221> sig_peptide
<222> (2)...(46)

<400> 6
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Met Gly Ala Val Trp Ser Ala Leu Leu Val Gly Gly Gly Leu Ala Gly
-15 -10 -5 1

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gcg ctc atc ctg tgg ctg ctg cgg gga gac tct ggg gcc ccg ggg aaa        97
Ala Leu Ile Leu Trp Leu Leu Arg Gly Asp Ser Gly Ala Pro Gly Lys
            5                   10                  15

gac ggg gtt gcg gag ccg ccg cag aag ggc gca cct cct ggg gag gct       145
Asp Gly Val Ala Glu Pro Pro Gln Lys Gly Ala Pro Pro Gly Glu Ala
        20                  25                  30

gcg gcc ccg gga gac ggt ccg ggt ggt ggt ggc agt ggc ggc ctg agc       193
Ala Ala Pro Gly Asp Gly Pro Gly Gly Gly Gly Ser Gly Gly Leu Ser
    35                  40                  45

cct gaa cct tcc gat cgg gag ctg gtc tcc aaa gca gag cat ctt cga       241
Pro Glu Pro Ser Asp Arg Glu Leu Val Ser Lys Ala Glu His Leu Arg
50                  55                  60                  65

gaa agc aac gga cat ttg att tct gag agc aaa gat ctt ggt aac ctg       289
Glu Ser Asn Gly His Leu Ile Ser Glu Ser Lys Asp Leu Gly Asn Leu
                70                  75                  80

ccg gaa gca cag cgg ctg cag aat gtt gga gca gac tgg gtc aat gcc       337
Pro Glu Ala Gln Arg Leu Gln Asn Val Gly Ala Asp Trp Val Asn Ala
            85                  90                  95

aga gag ttt gtt cct gtt ggg aag att cca gac aca cac tcc agg gcc       385
Arg Glu Phe Val Pro Val Gly Lys Ile Pro Asp Thr His Ser Arg Ala
        100                 105                 110

gac tct gaa gcg gca aga aat caa agc cca gga tct cat gga gga gaa       433
Asp Ser Glu Ala Ala Arg Asn Gln Ser Pro Gly Ser His Gly Gly Glu
    115                 120                 125

tgg aga ctc ccc aaa gga caa gaa aca gct gtc aaa gta gct ggc agt       481
Trp Arg Leu Pro Lys Gly Gln Glu Thr Ala Val Lys Val Ala Gly Ser
130                 135                 140                 145

gtg gcc gca aag ctg gcc tcc agc agc ctg ctt gtg gac aga gct aaa       529
Val Ala Ala Lys Leu Ala Ser Ser Ser Leu Leu Val Asp Arg Ala Lys
                150                 155                 160

gca gtc agt cag gac cag gca ggc cac gag gac tgg gaa gtg gtg tct       577
Ala Val Ser Gln Asp Gln Ala Gly His Glu Asp Trp Glu Val Val Ser
            165                 170                 175

agg cac tca tct tgg ggg agt gtt ggt ttg ggt ggc agt ctt gag gct       625
Arg His Ser Ser Trp Gly Ser Val Gly Leu Gly Gly Ser Leu Glu Ala
        180                 185                 190

tct agg tta agt cta aat cag aga atg gac gac agc aca aac agt ctt       673
Ser Arg Leu Ser Leu Asn Gln Arg Met Asp Asp Ser Thr Asn Ser Leu
    195                 200                 205

gtg gga gga aga ggc tgg gaa gta gat ggg aaa gtg gca tct ctg aaa       721
Val Gly Gly Arg Gly Trp Glu Val Asp Gly Lys Val Ala Ser Leu Lys
210                 215                 220                 225
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cct caa cag gtc agc atc cag ttc cag gtg cac tac acc aca aac acc 769
Pro Gln Gln Val Ser Ile Gln Phe Gln Val His Tyr Thr Thr Asn Thr
230 235 240

gat gtg cag ttc att gca gtg act gga gac cat gag agc ctt ggg aga 817
Asp Val Gln Phe Ile Ala Val Thr Gly Asp His Glu Ser Leu Gly Arg
245 250 255

tgg aac aca tac atc cca ctc cac tac tgc aaa gac ggg ctc tgg tct 865
Trp Asn Thr Tyr Ile Pro Leu His Tyr Cys Lys Asp Gly Leu Trp Ser
260 265 270

cat tct gtc ttc ctg cct gca gac aca gtg gtg gag tgg aag ttc gtg 913
His Ser Val Phe Leu Pro Ala Asp Thr Val Val Glu Trp Lys Phe Val
275 280 285

ttg gta gag aat aag gaa gtt act cgt tgg gaa gaa tgc agc aat aga 961
Leu Val Glu Asn Lys Glu Val Thr Arg Trp Glu Glu Cys Ser Asn Arg
290 295 300 305

ttc ctg cag act ggc cat gag gat aaa gtg gtt cat ggg tgg tgg ggg 1009
Phe Leu Gln Thr Gly His Glu Asp Lys Val Val His Gly Trp Trp Gly
310 315 320

att cac tgactcagtt ttcagagcat ccaagaggct gcagcagaat gtggacaagg 1065
Ile His

ctaaggcttt agagcgcact gcatagctta aagtaaaggc ggtgtgattc caattgtagc 1125
catcagggct ctttcagatt tgctagtgtg gcttttgtcc aaaatgtagg aagatgtatg 1185
cctgcagata atgcttcctg taanctggca cttgtccctt attgtattga ctggtttgtg 1245
ctgacacatc aggacttgag gaattgatca tcctgggtag ttgcatcttg ggtagtacac 1305
ctgaggtatg gactacatat gggcaaggag caactaagca actgcacggg tacaaggtag 1365
agcgccctta gcagctctta gactagaaag actacaataa gccccatcaa acacagctaa 1425
agcaacactg 1435

<210> 7
<211> 1131
<212> DNA
<213> Mouse

<400> 7
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tccatggcgt cgctcctgtg ctgtgggcct aagctggccg cctgtggcat cgtcctcagc 120
gcctggggag tgatcatgtt gataatgctc gggatatttt tcaatgtcca ttctgctgtg 180
ttaattgagg acgttccctt cacagagaaa gattttgaga acggtcctca gaacatatac 240
aacctgtacg agcaagtcag ctacaactgt ttcatcgccg cgggcctcta cctcctcctc 300
ggaggcttct ccttctgcca agttcgtctc aacaagcgca aggaatacat ggtgcgctag 360
agcgcggtcc gcctctccct ccccagcccc cttctctatt taaagactcc gcagactccg 420
tcccactcat ctggcgtcct ttgggacttg tgaccctagc gagacgtcat ccctggccct 480
gcaaaactgc gcccagcctc tggaggagac cgagggtgac cgcgccccgt tctgaactac 540
aataaaaaga agcggttccc cctaagcttg ctgtctgtgc tttcagggag gggcgggccc 600
gggctggaag gggctgagac cggcctcatc gaggagtccg gaccctccga cggaagtgga 660
atgaagctag ccggaagtga agcaacgtct tccacctcgt cttcctccgc gcggcgaggc 720
cccttgagtg actggggaga ggtcgggtct cggccaatca gctgcaggga gggcgggact 780
ttctgcgcgg gagcccgagc ggccggctgc cgggctctcc gtggtttcca gctcgcgtgg 840
tggtggtggc ggcggagcgt ctccgtgagg aggtgcgcgg ggccatgacg tcagcgtcca 900

ccaaggttgg agagatcttc tccgcggccg gcgccgcctt cacgaagctc ggggagttga 960
cgatgcagct gcatccagtc tcggactctt cccctgccgg tgccaagtgg acggagacgg 1020
agatagagat gctgagggct gctgtgaagc gctttgggga cgatcttaat cacatcagct 1080
gtgtcatcaa ggaacggaca gtggctcaga taaagaccac tgtgaagcga a 1131

<210> 8
<211> 1357
<212> DNA
<213> Mouse

<220>
<221> CDS
<222> (150)...(989)

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ggcagacagt cagaccgtct agcgggcctg gcttgcctac ctggcagctg cacccggtcc 120
ttcacccaga gctggttcca tagctcaac atg gtc ccc tgg ttc ctc ctg tct 173
Met Val Pro Trp Phe Leu Leu Ser
1 5

ctg ctg cta ctt gcg agg cct gtg cct ggg gtg gcc tac tct gtg tca 221
Leu Leu Leu Leu Ala Arg Pro Val Pro Gly Val Ala Tyr Ser Val Ser
10 15 20

ctc ccg gcc tcc ttc ctg gag gat gta gcc ggc agc ggg gaa gct gag 269
Leu Pro Ala Ser Phe Leu Glu Asp Val Ala Gly Ser Gly Glu Ala Glu
25 30 35 40

ggt tct tca gcc tct tcc ccg agc ctg ccg ccg cct ggg act cca gcc 317
Gly Ser Ser Ala Ser Ser Pro Ser Leu Pro Pro Pro Gly Thr Pro Ala
45 50 55

ttc agt ccc aca ccg gag aga ccc cag ccc aca gct ctg gac ggc ccc 365
Phe Ser Pro Thr Pro Glu Arg Pro Gln Pro Thr Ala Leu Asp Gly Pro
60 65 70

gtg cca ccc acc aac ctc ctg gaa ggg atc atg gat ttc ttc cgg cag 413
Val Pro Pro Thr Asn Leu Leu Glu Gly Ile Met Asp Phe Phe Arg Gln
75 80 85

tac gtg atg ctc atc gcg gtg gtg ggc tcg ctg acc ttc ctc atc atg 461
Tyr Val Met Leu Ile Ala Val Val Gly Ser Leu Thr Phe Leu Ile Met
90 95 100

ttc ata gtc tgc gcc gcc ctc atc acg cgc cag aag cac aag gcc aca 509
Phe Ile Val Cys Ala Ala Leu Ile Thr Arg Gln Lys His Lys Ala Thr
105 110 115 120

gcc tac tac cca tcc tcg ttc cct gaa aag aag tat gtg gac cag aga 557
Ala Tyr Tyr Pro Ser Ser Phe Pro Glu Lys Lys Tyr Val Asp Gln Arg
125 130 135

gac cgg gct ggg gga ccc cgt acc ttc agc gag gtc cct gac agg gca 605
Asp Arg Ala Gly Gly Pro Arg Thr Phe Ser Glu Val Pro Asp Arg Ala
140 145 150

cct gac agc cgg cat gaa gaa ggc ctg gac acc tcc cat cag ctc cag 653
Pro Asp Ser Arg His Glu Glu Gly Leu Asp Thr Ser His Gln Leu Gln
155 160 165

gct gac att ctg gct gct acc cag aac ctc cgg tct cca gct aga gcc 701
Ala Asp Ile Leu Ala Ala Thr Gln Asn Leu Arg Ser Pro Ala Arg Ala
170 175 180

ctg cca ggc aat ggg gag gga gca aag cct gtg aag ggt ggg tcg gag 749
Leu Pro Gly Asn Gly Glu Gly Ala Lys Pro Val Lys Gly Gly Ser Glu
185 190 195 200

gag gag gag gaa gag gtg ctc agc ggt cag gag gag gcc cag gaa gcc 797
Glu Glu Glu Glu Glu Val Leu Ser Gly Gln Glu Glu Ala Gln Glu Ala
205 210 215

cca gta tgt ggg gtc act gaa gag aag ctg ggg gtc cca gag gag tcg 845
Pro Val Cys Gly Val Thr Glu Glu Lys Leu Gly Val Pro Glu Glu Ser
220 225 230

gtc tca gca gag gct gaa ggg gtt cct gcc acc agt gag ggc caa ggg 893
Val Ser Ala Glu Ala Glu Gly Val Pro Ala Thr Ser Glu Gly Gln Gly
235 240 245

gaa gca gaa ggg tct ttc tcc tta gcc cag gaa tcc cag gga gca act 941
Glu Ala Glu Gly Ser Phe Ser Leu Ala Gln Glu Ser Gln Gly Ala Thr
250 255 260

ggt cct cct gaa agt ccc tgt gcc tgc aac aga gtc tcc ccc agt gtc 989
Gly Pro Pro Glu Ser Pro Cys Ala Cys Asn Arg Val Ser Pro Ser Val
265 270 275 280

taacaggccc cagaactgct gggacccgaa tgttgggtcc ttgagggtca cctctttggt 1049
caagaaaggc attcagctct aactgctcct tgataccacg tggcttggcc attgctggtg 1109
ccaaggctga ccccgaactg gcagagccga tgccctctgg tgcaccccag gaaacatctc 1169
cccaagttcc agcgccctta atgactcttg ccaccctggg ggcttcaccc taacgcacca 1229
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agaccaga 1357

<210> 9
<211> 815
<212> DNA
<213> Mouse

<220>
<221> CDS
<222> (119)...(682)

<221> sig_peptide
<222> (119)...(205)

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cggagagcag ctctgggcgc cgggcggttg ctgcgggcgc tcagggggccc tgggaaca 118
atg gcg ctg tgc gcg cgg gcc gcg ctg ctg ctg ggc gtg ctg cag gtg 166
Met Ala Leu Cys Ala Arg Ala Ala Leu Leu Leu Gly Val Leu Gln Val

-25 -20 -15

ctg gcg ctg cta ggg gcg gcg cag gac ccg acc gac gct cag ggc tct 214
Leu Ala Leu Leu Gly Ala Ala Gln Asp Pro Thr Asp Ala Gln Gly Ser
-10 -5 1

gca agt gga aac cac tca gtg ctg acc tcc aat att aac ata aca gag 262
Ala Ser Gly Asn His Ser Val Leu Thr Ser Asn Ile Asn Ile Thr Glu
5 10 15

aat acc aac cag acc atg agt gtg gtt tcc aac cag acc agt gaa atg 310
Asn Thr Asn Gln Thr Met Ser Val Val Ser Asn Gln Thr Ser Glu Met
20 25 30 35

cag agc acc gcg aag cct tcc gta ctg cca aaa act acc aca ctt atc 358
Gln Ser Thr Ala Lys Pro Ser Val Leu Pro Lys Thr Thr Thr Leu Ile
40 45 50

act gtg aaa cct gca act att gtt aaa ata tca acc cca gga gtc tta 406
Thr Val Lys Pro Ala Thr Ile Val Lys Ile Ser Thr Pro Gly Val Leu
55 60 65

cca cat gtg acg cct act gcc tca aag tct aca ccc aat gca agt gct 454
Pro His Val Thr Pro Thr Ala Ser Lys Ser Thr Pro Asn Ala Ser Ala
70 75 80

tct cca aac tct acc cac acg tca gca tcc atg aca acc cca gcc cac 502
Ser Pro Asn Ser Thr His Thr Ser Ala Ser Met Thr Thr Pro Ala His
85 90 95

agt agt tta ttg aca act gta acg gtt tca gca act act cat ccc acc 550
Ser Ser Leu Leu Thr Thr Val Thr Val Ser Ala Thr Thr His Pro Thr
100 105 110 115

aaa ggc aaa gga tcc aag ttt gat gcc ggc agc ttt gtt ggt ggt ata 598
Lys Gly Lys Gly Ser Lys Phe Asp Ala Gly Ser Phe Val Gly Gly Ile
120 125 130

ggt gtt aac act ggg agt ttt atc tat tct cta cat tgg atg caa aat 646
Gly Val Asn Thr Gly Ser Phe Ile Tyr Ser Leu His Trp Met Gln Asn
135 140 145

gta tta ttc aag aag agg cat tcg gta ccg aag cat tgacgaacat 692
Val Leu Phe Lys Lys Arg His Ser Val Pro Lys His
150 155

gatgccatca tttaaagtac ttcagtggtc aaggaaagaa gaaagactgc agccttatca 752
attattttgg tttatattag tttaaactat tattttcttg gaagtagtat aaacaagtca 812
tgc 815

<210> 10
<211> 1129
<212> DNA
<213> Mouse

<220>
<221> CDS

<222> (13)...(963)

<221> sig_peptide
<222> (13)...(90)

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Met Arg Ser Gly Ala Leu Trp Pro Leu Leu Trp Gly Ala
-25 -20 -15

ctg gtc tgg aca gtg gga tcc gtg ggc gcc gtg atg ggc tcc gag gat 99
Leu Val Trp Thr Val Gly Ser Val Gly Ala Val Met Gly Ser Glu Asp
-10 -5 1

tct gtg ccc ggt ggc gtg tgc tgg ctc cag cag ggc aga gag gcc acc 147
Ser Val Pro Gly Gly Val Cys Trp Leu Gln Gln Gly Arg Glu Ala Thr
5 10 15

tgc agt ctg gtg ctg aag act cgt gtc agc cgg gag gag tgc tgt gct 195
Cys Ser Leu Val Leu Lys Thr Arg Val Ser Arg Glu Glu Cys Cys Ala
20 25 30 35

tcc ggc aac atc aac acc gcc tgg tcc aac ttc acc cac cca ggc aat 243
Ser Gly Asn Ile Asn Thr Ala Trp Ser Asn Phe Thr His Pro Gly Asn
40 45 50

aaa atc agc ctg cta ggg ttc ctg ggc ctc gtc cac tgc ctc ccc tgc 291
Lys Ile Ser Leu Leu Gly Phe Leu Gly Leu Val His Cys Leu Pro Cys
55 60 65

aaa gat tcc tgc gac gga gtg gag tgc ggc ccc ggc aag gcg tgc cgc 339
Lys Asp Ser Cys Asp Gly Val Glu Cys Gly Pro Gly Lys Ala Cys Arg
70 75 80

aat gct ggg ggg gcg tcc aac aac tgc gag tgc gtg ccc aac tgc gag 387
Asn Ala Gly Gly Ala Ser Asn Asn Cys Glu Cys Val Pro Asn Cys Glu
85 90 95

ggg ttt ccc gcg ggc ttc cag gtc tgc ggc tct gat ggc gcc acc tac 435
Gly Phe Pro Ala Gly Phe Gln Val Cys Gly Ser Asp Gly Ala Thr Tyr
100 105 110 115

cgg gac gaa tgc gaa ctg cgc acc gcg cgc tgt cgc gga cac cca gac 483
Arg Asp Glu Cys Glu Leu Arg Thr Ala Arg Cys Arg Gly His Pro Asp
120 125 130

ttg cgc gtc atg tac cgc ggc cgc tgt caa aag tct tgc gct cag gta 531
Leu Arg Val Met Tyr Arg Gly Arg Cys Gln Lys Ser Cys Ala Gln Val
135 140 145

gtg tgc ccg cgt ccc cag tcg tgc ctt gtg gat cag acc ggc agc gca 579
Val Cys Pro Arg Pro Gln Ser Cys Leu Val Asp Gln Thr Gly Ser Ala
150 155 160

cac tgc gtg gtg tgt cgc gct gcg ccc tgc cca gta cct tcc aac ccc 627
His Cys Val Val Cys Arg Ala Ala Pro Cys Pro Val Pro Ser Asn Pro
165 170 175

ggc caa gaa ctc tgt ggc aac aac aac gtt acc tac atc tcg tcg tgt 675
Gly Gln Glu Leu Cys Gly Asn Asn Asn Val Thr Tyr Ile Ser Ser Cys
180 185 190 195

cac ctg cgc cag gcc act tgc ttc ctg ggc cgc tcc att ggg gtt cgg 723
His Leu Arg Gln Ala Thr Cys Phe Leu Gly Arg Ser Ile Gly Val Arg
200 205 210

cac cca ggc atc tgc aca ggt ggc ccc aag ttc ctg aag tct ggc gat 771
His Pro Gly Ile Cys Thr Gly Gly Pro Lys Phe Leu Lys Ser Gly Asp
215 220 225

gct gcc att gtt gat atg gtc cct ggc aag ccc atg tgt gtt gag agc 819
Ala Ala Ile Val Asp Met Val Pro Gly Lys Pro Met Cys Val Glu Ser
230 235 240

ttc tct gac tac cct cca ctt ggt cgc ttt gct gtt cgt gac atg agg 867
Phe Ser Asp Tyr Pro Pro Leu Gly Arg Phe Ala Val Arg Asp Met Arg
245 250 255

cag aca gtt gct gtg ggt gtc atc aaa gct gtg gac aag aag gct gct 915
Gln Thr Val Ala Val Gly Val Ile Lys Ala Val Asp Lys Lys Ala Ala
260 265 270 275

gga gct ggc aaa gtc acc aag tct gcc cag aaa gct cag aag gct aaa 963
Gly Ala Gly Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Lys
280 285 290

tgaatattac ccctaacacc tgccacccca gtcttaatca gtggtggaag aacggtctca 1023
gaactgtttg tctcaattgg ccatttaagt ttaatagtaa aagactggtt aatgataaca 1083
atgcatcgta aaaccttcag aaggaaagaa tgttgtggac catttt 1129

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<211> 196
<212> PRT
<213> Mouse

<400> 11
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1 5 10 15
Gln Val Leu Ser Leu Arg Asp Val Gly Leu Gly Ser Gly Ala Ala Glu
20 25 30
Met Asp Phe Ser Ala Phe Gly Asn Leu Arg Ala Leu Asp Leu Ser Gly
35 40 45
Asn Ser Leu Thr Ser Phe Gln Lys Phe Lys Gly Ser Leu Ala Leu Arg
50 55 60
Thr Leu Asp Leu Arg Arg Asn Ser Leu Thr Ala Leu Pro Gln Arg Val
65 70 75 80
Val Ser Glu Gln Pro Leu Arg Gly Leu Gln Thr Ile Tyr Leu Ser Gln
85 90 95
Asn Pro Tyr Asp Cys Cys Gly Val Glu Gly Trp Gly Ala Leu Gln Gln
100 105 110
His Phe Lys Thr Val Ala Asp Leu Ser Met Val Thr Cys Asn Leu Ser
115 120 125
Ser Lys Ile Val Arg Val Val Glu Leu Pro Glu Gly Leu Pro Gln Gly
130 135 140

Cys Lys Trp Glu Gln Val Asp Thr Gly Leu Phe Tyr Leu Val Leu Ile
145 150 155 160
Leu Pro Ser Cys Leu Thr Leu Leu Val Ala Cys Thr Val Val Phe Leu
165 170 175
Thr Phe Lys Lys Pro Leu Leu Gln Val Ile Lys Ser Arg Cys His Trp
180 185 190
Ser Ser Ile Tyr
195

<210> 12
<211> 174
<212> PRT
<213> Mouse

<400> 12
Met Ala Pro Ala Asn Leu Gly Leu Thr Pro His Trp Val Met Leu Leu
1 5 10 15
Gly Ala Val Leu Leu Leu Leu Leu Ser Gly Ala Ser Ala Gln Glu Pro
20 25 30
Pro Arg Val Gly Cys Ser Glu Tyr Thr Asn Arg Ser Cys Glu Glu Cys
35 40 45
Leu Arg Asn Val Ser Cys Leu Trp Cys Asn Glu Asn Lys Ala Cys Met
50 55 60
Asp Tyr Pro Val Arg Lys Ile Leu Pro Pro Ala Ser Leu Cys Lys Leu
65 70 75 80
Ser Ser Ala Arg Trp Gly Val Cys Trp Val Asn Phe Glu Ala Leu Ile
85 90 95
Ile Thr Met Ser Val Leu Gly Gly Ser Val Leu Leu Gly Ile Thr Val
100 105 110
Cys Cys Cys Tyr Cys Cys Arg Arg Lys Lys Ser Arg Lys Pro Asp Lys
115 120 125
Ser Asp Glu Arg Ala Met Arg Glu Gln Glu Glu Arg Arg Val Arg Gln
130 135 140
Glu Glu Arg Arg Ala Glu Met Lys Ser Arg His Asp Glu Ile Arg Lys
145 150 155 160
Lys Tyr Gly Leu Phe Lys Glu Gln Asn Pro Tyr Glu Lys Phe
165 170

<210> 13
<211> 106
<212> PRT
<213> Mouse

<400> 13
Ala Pro Gly Lys Pro Cys Arg Gly Leu Ser His Arg Thr Cys Ile Leu
1 5 10 15
Arg Cys Arg Pro Met Pro Leu Phe Thr His Pro Ser Pro Cys His Leu
20 25 30
Cys Gly Pro Cys Ser Thr Thr Ser Pro Ser Thr Trp Val Leu Cys Pro
35 40 45
Leu Pro Met Ser Pro Leu Cys Pro Thr Cys Val Ser Thr Met Thr Leu
50 55 60
Ala Thr Cys Thr Cys Pro Trp Ser Thr Thr Cys Pro Cys Thr Leu Ala
65 70 75 80
Pro Asn His Gly Ile Ala Ser Asp Thr Gln Ser Pro Val Ser Arg Ala
85 90 95
Glu Ser Val Gly Gly Pro Ser Leu Ile Phe

100 105

<210> 14
<211> 268
<212> PRT
<213> Mouse

<400> 14
Met Ala Leu Gly Phe Ser Gln Arg Ser Arg Met Val Ala Ala Gly Ala
1 5 10 15
Gly Val Thr Arg Leu Leu Val Leu Leu Leu Met Val Ala Ala Ala Pro
20 25 30
Ser Arg Ala Arg Gly Ser Gly Cys Arg Val Gly Ala Ser Ala Arg Gly
35 40 45
Thr Gly Ala Asp Gly Arg Glu Ala Glu Gly Cys Gly Thr Val Ala Leu
50 55 60
Leu Leu Glu His Ser Phe Glu Leu Gly Asp Gly Ala Asn Phe Gln Lys
65 70 75 80
Arg Gly Leu Leu Leu Trp Asn Gln Gln Asp Gly Thr Leu Ser Ala Thr
85 90 95
Gln Arg Gln Leu Ser Glu Glu Glu Arg Gly Arg Leu Arg Asp Val Ala
100 105 110
Ala Val Asn Gly Leu Tyr Arg Val Arg Val Pro Arg Arg Pro Gly Thr
115 120 125
Leu Asp Gly Ser Glu Ala Gly Gly His Val Ser Ser Phe Val Pro Ala
130 135 140
Cys Ser Leu Val Glu Ser His Leu Ser Asp Gln Leu Thr Leu His Val
145 150 155 160
Asp Val Ala Gly Asn Val Val Gly Leu Ser Val Val Val Tyr Pro Gly
165 170 175
Gly Cys Arg Gly Ser Glu Val Glu Asp Glu Asp Leu Glu Leu Phe Asn
180 185 190
Thr Ser Val Gln Leu Arg Pro Pro Ser Thr Ala Pro Gly Pro Glu Thr
195 200 205
Ala Ala Phe Ile Glu Arg Leu Glu Met Glu Gln Ala Gln Lys Ala Lys
210 215 220
Asn Pro Gln Glu Gln Lys Ser Phe Phe Ala Lys Tyr Trp Met Tyr Ile
225 230 235 240
Ile Pro Val Val Leu Phe Leu Met Met Ser Gly Ala Pro Asp Ala Gly
245 250 255
Gly Gln Gly Gly Gly Gly Gly Gly Gly Ser Ser Arg
260 265

<210> 15
<211> 66
<212> PRT
<213> Mouse

<400> 15
Met Asp Phe Leu Val Leu Phe Leu Phe Tyr Leu Ala Phe Leu Leu Ile
1 5 10 15
Cys Val Val Leu Ile Cys Ile Phe Thr Lys Ser Gln Arg Leu Lys Ala
20 25 30
Val Val Leu Gly Gly Ala Gln Val Ala Leu Val Leu Gly Tyr Cys Pro
35 40 45
Asp Val Asn Thr Val Leu Gly Ala Ser Leu Glu Gly Ser Gln Asp Lys
50 55 60

Gly Met
65

<210> 16
<211> 338
<212> PRT
<213> Mouse

<400> 16
Met Gly Ala Val Trp Ser Ala Leu Leu Val Gly Gly Gly Leu Ala Gly
1 5 10 15
Ala Leu Ile Leu Trp Leu Leu Arg Gly Asp Ser Gly Ala Pro Gly Lys
20 25 30
Asp Gly Val Ala Glu Pro Pro Gln Lys Gly Ala Pro Pro Gly Glu Ala
35 40 45
Ala Ala Pro Gly Asp Gly Pro Gly Gly Gly Gly Ser Gly Gly Leu Ser
50 55 60
Pro Glu Pro Ser Asp Arg Glu Leu Val Ser Lys Ala Glu His Leu Arg
65 70 75 80
Glu Ser Asn Gly His Leu Ile Ser Glu Ser Lys Asp Leu Gly Asn Leu
85 90 95
Pro Glu Ala Gln Arg Leu Gln Asn Val Gly Ala Asp Trp Val Asn Ala
100 105 110
Arg Glu Phe Val Pro Val Gly Lys Ile Pro Asp Thr His Ser Arg Ala
115 120 125
Asp Ser Glu Ala Ala Arg Asn Gln Ser Pro Gly Ser His Gly Gly Glu
130 135 140
Trp Arg Leu Pro Lys Gly Gln Glu Thr Ala Val Lys Val Ala Gly Ser
145 150 155 160
Val Ala Ala Lys Leu Ala Ser Ser Ser Leu Leu Val Asp Arg Ala Lys
165 170 175
Ala Val Ser Gln Asp Gln Ala Gly His Glu Asp Trp Glu Val Val Ser
180 185 190
Arg His Ser Ser Trp Gly Ser Val Gly Leu Gly Gly Ser Leu Glu Ala
195 200 205
Ser Arg Leu Ser Leu Asn Gln Arg Met Asp Asp Ser Thr Asn Ser Leu
210 215 220
Val Gly Gly Arg Gly Trp Glu Val Asp Gly Lys Val Ala Ser Leu Lys
225 230 235 240
Pro Gln Gln Val Ser Ile Gln Phe Gln Val His Tyr Thr Thr Asn Thr
245 250 255
Asp Val Gln Phe Ile Ala Val Thr Gly Asp His Glu Ser Leu Gly Arg
260 265 270
Trp Asn Thr Tyr Ile Pro Leu His Tyr Cys Lys Asp Gly Leu Trp Ser
275 280 285
His Ser Val Phe Leu Pro Ala Asp Thr Val Val Glu Trp Lys Phe Val
290 295 300
Leu Val Glu Asn Lys Glu Val Thr Arg Trp Glu Glu Cys Ser Asn Arg
305 310 315 320
Phe Leu Gln Thr Gly His Glu Asp Lys Val Val His Gly Trp Trp Gly
325 330 335
Ile His

<210> 17
<211> 119
<212> PRT

<213> Mouse

<400> 17

Gly Thr Ser Pro Ala Ser Val Leu Arg Ser Val Ser Ser Asp Pro Ser
1   5   10   15
Leu Pro Pro Pro Ser Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu
            20   25   30
Ala Ala Cys Gly Ile Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile
        35   40   45
Met Leu Gly Ile Phe Phe Asn Val His Ser Ala Val Leu Ile Glu Asp
    50   55   60
Val Pro Phe Thr Glu Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr
65   70   75   80
Asn Leu Tyr Glu Gln Val Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu
                85   90   95
Tyr Leu Leu Leu Gly Gly Phe Ser Phe Cys Gln Val Arg Leu Asn Lys
            100   105   110
Arg Lys Glu Tyr Met Val Arg
        115

<210> 18
<211> 280
<212> PRT
<213> Mouse

<400> 18

Met Val Pro Trp Phe Leu Leu Ser Leu Leu Leu Leu Ala Arg Pro Val
1   5   10   15
Pro Gly Val Ala Tyr Ser Val Ser Leu Pro Ala Ser Phe Leu Glu Asp
            20   25   30
Val Ala Gly Ser Gly Glu Ala Glu Gly Ser Ser Ala Ser Ser Pro Ser
        35   40   45
Leu Pro Pro Pro Gly Thr Pro Ala Phe Ser Pro Thr Pro Glu Arg Pro
    50   55   60
Gln Pro Thr Ala Leu Asp Gly Pro Val Pro Pro Thr Asn Leu Leu Glu
65   70   75   80
Gly Ile Met Asp Phe Phe Arg Gln Tyr Val Met Leu Ile Ala Val Val
                85   90   95
Gly Ser Leu Thr Phe Leu Ile Met Phe Ile Val Cys Ala Ala Leu Ile
            100   105   110
Thr Arg Gln Lys His Lys Ala Thr Ala Tyr Tyr Pro Ser Ser Phe Pro
        115   120   125
Glu Lys Lys Tyr Val Asp Gln Arg Asp Arg Ala Gly Gly Pro Arg Thr
    130   135   140
Phe Ser Glu Val Pro Asp Arg Ala Pro Asp Ser Arg His Glu Glu Gly
145   150   155   160
Leu Asp Thr Ser His Gln Leu Gln Ala Asp Ile Leu Ala Ala Thr Gln
                165   170   175
Asn Leu Arg Ser Pro Ala Arg Ala Leu Pro Gly Asn Gly Glu Gly Ala
            180   185   190
Lys Pro Val Lys Gly Gly Ser Glu Glu Glu Glu Glu Glu Val Leu Ser
        195   200   205
Gly Gln Glu Glu Ala Gln Glu Ala Pro Val Cys Gly Val Thr Glu Glu
    210   215   220
Lys Leu Gly Val Pro Glu Glu Ser Val Ser Ala Glu Ala Glu Gly Val
225   230   235   240
Pro Ala Thr Ser Glu Gly Gln Gly Glu Ala Glu Gly Ser Phe Ser Leu

245 250 255
Ala Gln Glu Ser Gln Gly Ala Thr Gly Pro Pro Glu Ser Pro Cys Ala
260 265 270
Cys Asn Arg Val Ser Pro Ser Val
275 280

<210> 19
<211> 188
<212> PRT
<213> Mouse

<400> 19
Met Ala Leu Cys Ala Arg Ala Ala Leu Leu Leu Gly Val Leu Gln Val
1 5 10 15
Leu Ala Leu Leu Gly Ala Ala Gln Asp Pro Thr Asp Ala Gln Gly Ser
20 25 30
Ala Ser Gly Asn His Ser Val Leu Thr Ser Asn Ile Asn Ile Thr Glu
35 40 45
Asn Thr Asn Gln Thr Met Ser Val Val Ser Asn Gln Thr Ser Glu Met
50 55 60
Gln Ser Thr Ala Lys Pro Ser Val Leu Pro Lys Thr Thr Thr Leu Ile
65 70 75 80
Thr Val Lys Pro Ala Thr Ile Val Lys Ile Ser Thr Pro Gly Val Leu
85 90 95
Pro His Val Thr Pro Thr Ala Ser Lys Ser Thr Pro Asn Ala Ser Ala
100 105 110
Ser Pro Asn Ser Thr His Thr Ser Ala Ser Met Thr Thr Pro Ala His
115 120 125
Ser Ser Leu Leu Thr Thr Val Thr Val Ser Ala Thr Thr His Pro Thr
130 135 140
Lys Gly Lys Gly Ser Lys Phe Asp Ala Gly Ser Phe Val Gly Gly Ile
145 150 155 160
Gly Val Asn Thr Gly Ser Phe Ile Tyr Ser Leu His Trp Met Gln Asn
165 170 175
Val Leu Phe Lys Lys Arg His Ser Val Pro Lys His
180 185

<210> 20
<211> 317
<212> PRT
<213> Mouse

<400> 20
Met Arg Ser Gly Ala Leu Trp Pro Leu Leu Trp Gly Ala Leu Val Trp
1 5 10 15
Thr Val Gly Ser Val Gly Ala Val Met Gly Ser Glu Asp Ser Val Pro
20 25 30
Gly Gly Val Cys Trp Leu Gln Gln Gly Arg Glu Ala Thr Cys Ser Leu
35 40 45
Val Leu Lys Thr Arg Val Ser Arg Glu Glu Cys Cys Ala Ser Gly Asn
50 55 60
Ile Asn Thr Ala Trp Ser Asn Phe Thr His Pro Gly Asn Lys Ile Ser
65 70 75 80
Leu Leu Gly Phe Leu Gly Leu Val His Cys Leu Pro Cys Lys Asp Ser
85 90 95
Cys Asp Gly Val Glu Cys Gly Pro Gly Lys Ala Cys Arg Asn Ala Gly
100 105 110

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Gly Ala Ser Asn Asn Cys Glu Cys Val Pro Asn Cys Glu Gly Phe Pro
        115                 120                 125
Ala Gly Phe Gln Val Cys Gly Ser Asp Gly Ala Thr Tyr Arg Asp Glu
    130                 135                 140
Cys Glu Leu Arg Thr Ala Arg Cys Arg Gly His Pro Asp Leu Arg Val
145                 150                 155                 160
Met Tyr Arg Gly Arg Cys Gln Lys Ser Cys Ala Gln Val Val Cys Pro
                165                 170                 175
Arg Pro Gln Ser Cys Leu Val Asp Gln Thr Gly Ser Ala His Cys Val
            180                 185                 190
Val Cys Arg Ala Ala Pro Cys Pro Val Pro Ser Asn Pro Gly Gln Glu
        195                 200                 205
Leu Cys Gly Asn Asn Asn Val Thr Tyr Ile Ser Ser Cys His Leu Arg
    210                 215                 220
Gln Ala Thr Cys Phe Leu Gly Arg Ser Ile Gly Val Arg His Pro Gly
225                 230                 235                 240
Ile Cys Thr Gly Gly Pro Lys Phe Leu Lys Ser Gly Asp Ala Ala Ile
                245                 250                 255
Val Asp Met Val Pro Gly Lys Pro Met Cys Val Glu Ser Phe Ser Asp
            260                 265                 270
Tyr Pro Pro Leu Gly Arg Phe Ala Val Arg Asp Met Arg Gln Thr Val
        275                 280                 285
Ala Val Gly Val Ile Lys Ala Val Asp Lys Lys Ala Ala Gly Ala Gly
    290                 295                 300
Lys Val Thr Lys Ser Ala Gln Lys Ala Gln Lys Ala Lys
305                 310                 315
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